HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use docetaxel injection concentrate safely and effectively. See full prescribing information for docetaxel injection concentrate.

Docetaxel Injection Concentrate
Intravenous Infusion (IV)
Initial U.S. Approval: 1996

WARNING: TOXIC DEATHS, HEPATOTOXICITY, NEUTROPENIA, HYPERSENSITIVITY REACTIONS, and FLUID RETENTION
See full prescribing information for complete boxed warning

- **Treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with NSCLC and prior platinum-based therapy receiving docetaxel injection concentrate at 100 mg/m^2 (5.1)**
- **Should not be given if bilirubin >ULN, or if AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN. LFT elevations increase risk of severe or life-threatening complications. Obtain LFTs before each treatment cycle (8.6)**
- **Should not be given if neutrophil counts are <1500 cells/mm^3. Obtain frequent blood counts to monitor for neutropenia (4)**
- **Severe hypersensitivity, including very rare fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Severe reactions require immediate discontinuation of docetaxel injection concentrate and administration of appropriate therapy (5.4)**
- **Contraindicated if history of severe hypersensitivity reactions to docetaxel injection concentrate or to drugs formulated with polysorbate 80 (4)**
- **Severe fluid retention may occur despite dexamethasone (5.5)**

----------INDICATIONS AND USAGE----------
Docetaxel injection concentrate is a microtubule inhibitor indicated for:

- **Breast Cancer (BC):** single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC (1.1)
- **Non-Small Cell Lung Cancer (NSCLC):** single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC (1.2)
- **Hormone Refractory Prostate Cancer (HRPC):** with prednisone in androgen independent (hormone refractory) metastatic prostate cancer (1.3)
- **Gastric Adenocarcinoma (GC):** with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction (1.4)
- **Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN):** with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN (1.5)

----------DOSAGE AND ADMINISTRATION----------
Administer in a facility equipped to manage possible complications (e.g., anaphylaxis). Administer intravenously (IV) over 1 hr every 3 weeks. PVC equipment is not recommended. **Use only a 21 gauge needle to withdraw docetaxel injection concentrate from the vial.**

- **BC locally advanced or metastatic:** 60 mg/m^2 to 100 mg/m^2 single agent (2.1)
- **BC adjuvant:** 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles (2.1)
- **NSCLC:** after platinum therapy failure: 75 mg/m^2 single agent (2.2)
- **NSCLC:** chemotherapy-naive: 75 mg/m^2 followed by cisplatin 75 mg/m^2 (2.2)
- **HRPC:** 75 mg/m^2 with 5 mg prednisone twice a day continuously (2.3)
- **GC:** 75 mg/m^2 followed by cisplatin 75 mg/m^2 (both on day 1 only) followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1 to 5), starting at end of cisplatin infusion (2.4)
- **SCCHN:** 75 mg/m^2 followed by cisplatin 75 mg/m^2 IV (day 1), followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1 to 5), starting at end of cisplatin infusion; for 4 cycles (2.5)
- **SCCHN:** 75 mg/m^2 followed by cisplatin 100 mg/m^2 IV (day 1), followed by fluorouracil 1000 mg/m^2 per day as a 24-hr IV (days 1 to 4); for 3 cycles (2.5)

For all patients:

- Premedicate with oral corticosteroids (2.6)
- Adjust dose as needed (2.7)

----------DOSAGE FORMS AND STRENGTHS----------

- One vial docetaxel injection concentrate: Single use vials 20 mg/mL, 80 mg/4 mL and 140 mg /7 mL (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to docetaxel or polysorbate 80 (4)
- Neutrophil counts of <1500 cells/mm^3 (4)

----------WARNINGS AND PRECAUTIONS----------

- **Acute myeloid leukemia:** In patients who received docetaxel injection concentrate, doxorubicin and cyclophosphamide, monitor for delayed myelodysplasia or myeloid leukemia (5.6).
- **Cutaneous reactions:** Reactions including erythema of the extremities with edema followed by desquamation may occur. Severe skin toxicity may require dose adjustment (5.7).
- **Neurologic reactions:** Reactions including. paresthesia, dysesthesia, and pain may occur. Severe neurosensory symptoms require dose adjustment or discontinuation if persistent (5.8).
- **Asthenia:** Severe asthenia may occur and may require treatment discontinuation (5.9).
- **Pregnancy:** Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant when receiving docetaxel injection concentrate (5.10, 8.1).

----------ADVERSE REACTIONS----------
Most common adverse reactions across all docetaxel injection concentrate indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, myalgia (6).

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1-800-432-8534 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter docetaxel metabolism (7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

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FULL PRESCRIBING INFORMATION

WARNING: TOXIC DEATHS, HEPATOTOXICITY, NEUTROPENIA, HYPERSENSITIVITY REACTIONS, and FLUID RETENTION

The incidence of treatment-related mortality associated with docetaxel injection concentrate therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive docetaxel injection concentrate as a single agent at a dose of 100 mg/m^2 *[see Warnings and Precautions (5.1)]*.
Docetaxel injection concentrate should not be given to patients with bilirubin >upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase >1.5 x ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, AST or ALT, and alkaline phosphatase values should be obtained prior to each cycle of docetaxel injection concentrate therapy *[see Warnings and Precautions (5.2)]*. Docetaxel injection concentrate therapy should not be given to patients with neutrophil counts of <1500 cells/mm^3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving docetaxel injection concentrate *[see Warnings and Precautions (5.3)]*.
Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients who received a 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the docetaxel injection concentrate infusion and administration of appropriate therapy *[see Warnings and Precautions (5.4)]*. Docetaxel injection concentrate must not be given to patients who have a history of severe hypersensitivity reactions to docetaxel injection concentrate or to other drugs formulated with polysorbate 80 *[see Contraindications (4)]*.
Severe fluid retention occurred in 6.5% (6/92) of patients despite use of a 3-day dexamethasone premedication regimen. It was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites) *[see Warnings and Precautions (5.5)]*.

1. INDICATIONS AND USAGE

1.1 Breast Cancer

Docetaxel injection concentrate is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

Docetaxel injection concentrate in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

1.2 Non-Small Cell Lung Cancer

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Docetaxel injection concentrate as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.

Docetaxel injection concentrate in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

1.3 Prostate Cancer
Docetaxel injection concentrate in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

1.4 Gastric Adenocarcinoma
Docetaxel injection concentrate in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

1.5 Head and Neck Cancer
Docetaxel injection concentrate in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

2. DOSAGE AND ADMINISTRATION
For all indications, toxicities may warrant dosage adjustments *[see Dosage and Administration (2.7)]*.

Administer in a facility equipped to manage possible complications (e.g. anaphylaxis).

2.1 Breast Cancer
- For locally advanced or metastatic breast cancer after failure of prior chemotherapy, the recommended dose of docetaxel injection concentrate is 60 mg/m^2 to 100 mg/m^2 administered intravenously over 1 hour every 3 weeks.
- For the adjuvant treatment of operable node-positive breast cancer, the recommended docetaxel injection concentrate dose is 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities *[see Dosage and Administration (2.7)]*.

2.2 Non-Small Cell Lung Cancer
- For treatment after failure of prior platinum-based chemotherapy, docetaxel injection concentrate was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials *[see Boxed Warning, Dosage and Administration (2.7), Warnings and Precautions (5), Clinical Studies (14)]*.
- For chemotherapy-naïve patients, docetaxel injection concentrate was evaluated in combination with cisplatin. The recommended dose of docetaxel injection concentrate is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30 to 60 minutes every 3 weeks *[see Dosage and Administration (2.7)]*.

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2.3 Prostate Cancer

- For hormone-refractory metastatic prostate cancer, the recommended dose of docetaxel injection concentrate is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion. Prednisone 5 mg orally twice daily is administered continuously *[see Dosage and Administration (2.7)]*.

2.4 Gastric Adenocarcinoma

- For gastric adenocarcinoma, the recommended dose of docetaxel injection concentrate is 75 mg/m^2 as a 1 hour intravenous infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m^2 per day given as a 24-hour continuous intravenous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration *[see Dosage and Administration (2.7)]*.

2.5 Head and Neck Cancer

Patients must receive premedication with antiemetics, and appropriate hydration (prior to and after cisplatin administration). Prophylaxis for neutropenic infections should be administered. All patients treated on the docetaxel injection concentrate containing arms of the TAX323 and TAX324 studies received prophylactic antibiotics.

- *Induction chemotherapy followed by radiotherapy (TAX323)*
  For the induction treatment of locally advanced inoperable SCCHN, the recommended dose of docetaxel injection concentrate is 75 mg/m^2 as a 1 hour intravenous infusion followed by cisplatin 75 mg/m^2 intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy. *[see Dosage and Administration (2.7)]*.

- *Induction chemotherapy followed by chemoradiotherapy (TAX324)*
  For the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN, the recommended dose of docetaxel injection concentrate is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, patients should receive chemoradiotherapy *[see Dosage and Administration (2.7)]*.

2.6 Premedication Regimen

All patients should be premedicated with oral corticosteroids (see below for prostate cancer) such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day prior to docetaxel injection concentrate administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions *[see Boxed Warning, Warnings and Precautions (5.4)]*.

For hormone-refractory metastatic prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the docetaxel injection concentrate infusion *[see Warnings and Precautions (5.4)]*.

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2.7 Dosage Adjustments During Treatment

Breast Cancer

Patients who are dosed initially at 100 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, or severe or cumulative cutaneous reactions during docetaxel injection concentrate therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2 or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m^2 and who do not experience febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during docetaxel injection concentrate therapy may tolerate higher doses. Patients who develop ≥grade 3 peripheral neuropathy should have docetaxel injection concentrate treatment discontinued entirely.

Combination Therapy with Docetaxel Injection Concentrate in the Adjuvant Treatment of Breast Cancer

Docetaxel injection concentrate in combination with doxorubicin and cyclophosphamide should be administered when the neutrophil count is ≥1,500 cells/mm^3. Patients who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their docetaxel injection concentrate dose reduced to 60 mg/m^2. Patients who experience grade 3 or 4 stomatitis should have their docetaxel injection concentrate dose decreased to 60 mg/m^2. Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during docetaxel injection concentrate therapy should have their dosage of docetaxel injection concentrate reduced from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, treatment should be discontinued.

Non-Small Cell Lung Cancer

Monotherapy with docetaxel injection concentrate for NSCLC treatment after failure of prior platinum-based chemotherapy

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during docetaxel injection concentrate treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop ≥grade 3 peripheral neuropathy should have docetaxel injection concentrate treatment discontinued entirely.

Combination therapy with docetaxel injection concentrate for chemotherapy-naïve NSCLC

For patients who are dosed initially at docetaxel injection concentrate 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <25,000 cells/mm^3, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the docetaxel injection concentrate dosage in subsequent cycles should be reduced to 65 mg/m^2. In patients who require a further dose reduction, a dose of 50 mg/m^2 is recommended. For cisplatin dosage adjustments, see manufacturers' prescribing information.

Prostate Cancer

Combination therapy with docetaxel injection concentrate for hormone-refractory metastatic prostate cancer

Docetaxel injection concentrate should be administered when the neutrophil count is ≥1,500 cells/mm^3. Patients who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one week,

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severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during docetaxel injection concentrate therapy should have the dosage of docetaxel injection concentrate reduced from 75 mg/m² to 60 mg/m². If the patient continues to experience these reactions at 60 mg/m², the treatment should be discontinued.

Gastric or Head and Neck Cancer

Docetaxel injection concentrate in combination with cisplatin and fluorouracil in gastric cancer or head and neck cancer

Patients treated with docetaxel injection concentrate in combination with cisplatin and fluorouracil must receive antiemetics and appropriate hydration according to current institutional guidelines. In both studies, G-CSF was recommended during the second and/or subsequent cycles in case of febrile neutropenia, or documented infection with neutropenia, or neutropenia lasting more than 7 days. If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the docetaxel injection concentrate dose should be reduced from 75 mg/m^2 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the docetaxel injection concentrate dose should be reduced from 60 mg/m^2 to 45 mg/m^2. In case of grade 4 thrombocytopenia the docetaxel injection concentrate dose should be reduced from 75 mg/m^2 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of docetaxel injection concentrate until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. Discontinue treatment if these toxicities persist. *[see Warnings and Precautions (5.3)]*.

Recommended dose modifications for toxicities in patients treated with docetaxel injection concentrate in combination with cisplatin and fluorouracil are shown in Table 1.

Table 1 - Recommended Dose Modifications for Toxicities in Patients Treated with Docetaxel Injection Concentrate in Combination with Cisplatin and Fluorouracil

Toxicity	Dosage adjustment
Diarrhea grade 3	First episode: reduce fluorouracil dose by 20%. Second episode: then reduce docetaxel injection concentrate dose by 20%.
Diarrhea grade 4	First episode: reduce docetaxel injection concentrate and fluorouracil doses by 20%. Second episode: discontinue treatment.
Stomatitis/mucositis grade 3	First episode: reduce fluorouracil dose by 20%. Second episode: stop fluorouracil only, at all subsequent cycles. Third episode: reduce docetaxel injection concentrate dose by 20%.
Stomatitis/mucositis grade 4	First episode: stop fluorouracil only, at all subsequent cycles. Second episode: reduce docetaxel injection concentrate dose by 20%.

Liver dysfunction:

In case of AST/ALT >2.5 to ≤5 x ULN and AP ≤2.5 x ULN, or AST/ALT >1.5 to ≤5 x ULN and AP >2.5 to ≤5 x ULN, docetaxel injection concentrate should be reduced by 20%.

In case of AST/ALT >5 x ULN and/or AP >5 x ULN docetaxel injection concentrate should be stopped.

The dose modifications for cisplatin and fluorouracil in the gastric cancer study are provided

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below:

Cisplatin dose modifications and delays

Peripheral neuropathy: A neurological examination should be performed before entry into the study, and then at least every 2 cycles and at the end of treatment. In the case of neurological signs or symptoms, more frequent examinations should be performed and the following dose modifications can be made according to NCIC-CTC grade:

- Grade 2: Reduce cisplatin dose by 20%.
- Grade 3: Discontinue treatment.

Ototoxicity: In the case of grade 3 toxicity, discontinue treatment.

Nephrotoxicity: In the event of a rise in serum creatinine ≥grade 2 (>1.5 x normal value) despite adequate rehydration, CrCl should be determined before each subsequent cycle and the following dose reductions should be considered (see Table 2).

For other cisplatin dosage adjustments, also refer to the manufacturers' prescribing information.

Table 2 – Dose Reductions for Evaluation of Creatinine Clearance

Creatinine clearance result before next cycle	Cisplatin dose next cycle
CrCl ≥60 mL/min	Full dose of cisplatin was given. CrCl was to be repeated before each treatment cycle.
CrCl between 40 and 59 mL/min	Dose of cisplatin was reduced by 50% at subsequent cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was reinstituted at the next cycle. If no recovery was observed, then cisplatin was omitted from the next treatment cycle.
CrCl <40 mL/min	Dose of cisplatin was omitted in that treatment cycle only. If CrCl was still <40 mL/min at the end of cycle, cisplatin was discontinued. If CrCl was >40 and <60 mL/min at end of cycle, a 50% cisplatin dose was given at the next cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was given at next cycle.

CrCl = Creatinine clearance

Fluorouracil dose modifications and treatment delays

For diarrhea and stomatitis, see Table 1.

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In the event of grade 2 or greater plantar-palmar toxicity, fluorouracil should be stopped until recovery. The fluorouracil dosage should be reduced by 20%.

For other greater than grade 3 toxicities, except alopecia and anemia, chemotherapy should be delayed (for a maximum of 2 weeks from the planned date of infusion) until resolution to grade ≤1 and then recommenced, if medically appropriate.

For other fluorouracil dosage adjustments, also refer to the manufacturers' prescribing information.

Combination Therapy with Strong CYP3A4 inhibitors:
Avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors. Based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, consider a 50% docetaxel dose reduction if patients require co-administration of a strong CYP3A4 inhibitor *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

2.8 Administration Precautions
Docetaxel injection concentrate is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel injection concentrate solutions. The use of gloves is recommended. Please refer to *[see How Supplied/ Storage and Handling (16.3)]*.

If docetaxel injection concentrate, or diluted infusion solution should come into contact with the skin or mucosa, wash immediately and thoroughly with soap and water.

Do not use plasticized PVC equipment or devices that comes in direct contact with docetaxel injection solution during preparation and administration of docetaxel injection solutions for infusion. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may leach from PVC infusion bags or sets, the diluted docetaxel infusion solution should be stored in bottles made of glass, polypropylene or plastic bags made with polypropylene, polyolefin and administered through polyethylene-lined administration sets.

<u>One-vial Docetaxel Injection Concentrate</u>
Docetaxel injection concentrate requires no prior dilution with a diluent and is ready to be added to the infusion solution.

Please follow the preparation instructions provided below.

2.9 Preparation and Administration
Do not use the two-vial formulation (Injection Concentrate and diluent) with the one-vial formulation.

<u>One-vial Docetaxel Injection Concentrate</u>
Docetaxel injection concentrate (20 mg/mL) requires no prior dilution with a diluent and is ready to add to the infusion solution. Use only a 21 gauge needle to withdraw docetaxel injection concentrate from

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the vial because larger bore needles (e.g., 18 and 19 gauge) may result in stopper coring and rubber particulates.

1. Docetaxel injection concentrate vials should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) protected from light.
2. Using **only** a 21 gauge needle, aseptically withdraw the required amount of docetaxel injection concentrate (20 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL. If a dose greater than 200 mg of docetaxel injection concentrate is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL docetaxel injection concentrate is not exceeded
3. Thoroughly mix the infusion solution by gentle manual rotation.
4. As with all parenteral products, docetaxel injection concentrate should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel injection concentrate dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.

The docetaxel injection concentrate dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature (below 25°C) and lighting conditions.

2.10 Stability

Docetaxel injection concentrate dilution for infusion is stable for 4 hours, if stored between 2°C and 25°C (36°F and 77°F). Docetaxel injection concentrate dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour intravenous administration).

3. DOSAGE FORMS AND STRENGTHS

One-vial Docetaxel Injection Concentrate

Docetaxel Injection Concentrate is available as 20 mg/mL, 80 mg/4 mL and 140 mg /7 mL. Each mL contains 20 mg docetaxel, citric acid anhydrous (6 mg), Povidone (kollidon 12 PF) (100 mg), polysorbate 80 (424 mg) and ethanol (400 mg/mL).

4. CONTRAINDICATIONS

- Docetaxel injection concentrate is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Severe reactions, including anaphylaxis, have occurred *[see Warnings and Precautions (5.4)]*.
- Docetaxel injection concentrate should not be used in patients with neutrophil counts of <1500 cells/mm^3.

5. WARNINGS AND PRECAUTIONS

5.1 Toxic Deaths

Breast Cancer

Docetaxel injection concentrate administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of patients with various tumor types who had abnormal baseline liver function (AST and/or ALT >1.5 times ULN

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together with AP >2.5 times ULN). Among patients dosed at 60 mg/m^2, mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.

Non-Small Cell Lung Cancer

Docetaxel injection concentrate administered at a dose of 100 mg/m^2 in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75 mg/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had an ECOG PS of 2 at study entry *[see Dosage and Administration (2.2), Clinical Studies (14)]*.

5.2 Hepatic Impairment

Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with Docetaxel Injection Concentrate *[see Boxed Warning, Use in Specific Populations (8.6), Clinical studies (14)]*.

5.3 Hematologic Effects

Perform frequent peripheral blood cell counts on all patients receiving docetaxel injection concentrate. Patients should not be retreated with subsequent cycles of docetaxel injection concentrate until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3.

A 25% reduction in the dose of docetaxel injection concentrate is recommended during subsequent cycles following severe neutropenia (<500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a docetaxel injection concentrate cycle *[see Dosage and Administration (2.7)]*.

Neutropenia (<2000 neutrophils/mm^3) occurs in virtually all patients given 60 mg/m^2 to 100 mg/m^2 of docetaxel injection concentrate and grade 4 neutropenia (<500 cells/mm^3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^2. Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. Docetaxel injection concentrate should not be administered to patients with neutrophils <1500 cells/mm^3.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m^2 but was very uncommon in patients given 60 mg/m^2. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related *[see Adverse Reactions (6.1), Clinical Studies (14)]*.

Three breast cancer patients with severe liver impairment (bilirubin >1.7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia. In gastric cancer patients treated with docetaxel in combination with cisplatin and fluorouracil (TCF), febrile neutropenia and/or neutropenic infection occurred in 12% of patients receiving G-CSF compared to 28% who did not. Patients receiving TCF should be closely monitored during the first and subsequent cycles for febrile neutropenia and neutropenic infection *[see Dosage and Administration (2.7), Adverse Reactions (6)]*.

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5.4 Hypersensitivity Reactions

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the docetaxel injection concentrate infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with docetaxel injection concentrate.

Hypersensitivity reactions may occur within a few minutes following initiation of a docetaxel injection concentrate infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of docetaxel injection concentrate *[see Dosage and Administration (2.6)]*.

5.5 Fluid Retention

Severe fluid retention has been reported following docetaxel injection concentrate therapy. Patients should be premedicated with oral corticosteroids prior to each docetaxel injection concentrate administration to reduce the incidence and severity of fluid retention *[see Dosage and Administration (2.6)]*. Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m^2. Nine of 92 patients (9.8%) of patients discontinued treatment due to fluid retention: 4 patients discontinued with severe fluid retention; the remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m^2. Fluid retention was completely, but sometimes slowly, reversible with a median of 16 weeks from the last infusion of docetaxel injection concentrate to resolution (range: 0 to 42+ weeks). Patients developing peripheral edema may be treated with standard measures, e.g., salt restriction, oral diuretic(s).

5.6 Acute Myeloid Leukemia

Treatment-related acute myeloid leukemia (AML) or myelodysplasia has occurred in patients given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. In the adjuvant breast cancer trial *(TAX316)* AML occurred in 3 of 744 patients who received docetaxel injection concentrate, doxorubicin and cyclophosphamide (TAC) and in 1 of 736 patients who received fluorouracil, doxorubicin and cyclophosphamide *[see Clinical Studies (14.2)]*. In TAC-treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow-up.

5.7 Cutaneous Reactions

Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended *[see Dosage and Administration (2.7)]*. The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients.

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Among 92 breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued docetaxel injection concentrate due to skin toxicity.

5.8 Neurologic Reactions

Severe neurosensory symptoms (e.g. paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued *[see Dosage and Administration (2.7)]*. Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

5.9 Asthenia

Severe asthenia has been reported in 14.9% (144/965) of metastatic breast cancer patients but has led to treatment discontinuation in only 1.8%. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

5.10 Use in Pregnancy

Docetaxel injection concentrate can cause fetal harm when administered to a pregnant woman. Docetaxel caused embryofetal toxicities including intrauterine mortality when administered to pregnant rats and rabbits during the period of organogenesis. Embryofetal effects in animals occurred at doses as low as 1/50 and 1/300 the recommended human dose on a body surface area basis.

There are no adequate and well-controlled studies in pregnant women using docetaxel injection concentrate. If docetaxel injection concentrate is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with docetaxel injection concentrate *[see Use in Specific Populations (8.1)]*.

6. ADVERSE REACTIONS

The most serious adverse reactions from docetaxel injection concentrate are:

- Toxic Deaths *[see Boxed Warning, Warning and Precautions (5.1)]*
- Hepatotoxicity *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Neutropenia *[see Boxed Warning, Warnings and Precautions (5.3)]*
- Hypersensitivity *[see Boxed Warning, Warnings and Precautions (5.4)]*
- Fluid Retention *[see Boxed Warning, Warnings and Precautions (5.5)]*

The most common adverse reactions across all docetaxel injection concentrate indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Incidence varies depending on the indication.

Adverse reactions are described according to indication. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be

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directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy, and treatment-related side effects has not been established.

6.1 Clinical Trial Experience

Breast Cancer

Monotherapy with Docetaxel injection concentrate for locally advanced or metastatic breast cancer after failure of prior chemotherapy

Docetaxel injection concentrate 100 mg/m^2: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received docetaxel injection concentrate administered at 100 mg/m^2 as a 1-hour infusion every 3 weeks: 2045 patients with various tumor types and normal baseline liver function tests; the subset of 965 patients with locally advanced or metastatic breast cancer, both previously treated and untreated with chemotherapy, who had normal baseline liver function tests; and an additional 61 patients with various tumor types who had abnormal liver function tests at baseline. These reactions were described using COSTART terms and were considered possibly or probably related to docetaxel injection concentrate. At least 95% of these patients did not receive hematopoietic support. The safety profile is generally similar in patients receiving docetaxel injection concentrate for the treatment of breast cancer and in patients with other tumor types (See Table 3).

Table 3 - Summary of Adverse Reactions in Patients Receiving Docetaxel Injection Concentrate at 100 mg/m^2

Adverse Reaction	**All Tumor Types Normal LFTs* n=2045 %**	**All Tumor Types Elevated LFTs** n=61 %**	**Breast Cancer Normal LFTs* n=965 %**
Hematologic			
Neutropenia			
<2000 cells/mm^3	96	96	99
<500 cells/mm^3	75	88	86
Leukopenia			
<4000 cells/mm^3	96	98	99
<1000 cells/mm^3	32	47	44
Thrombocytopenia			
<100,000 cells/mm^3	8	25	9
Anemia			
<11 g/dL	90	92	94
<8 g/dL	9	31	8
Febrile Neutropenia***	11	26	12
Septic Death	2	5	1
Non-Septic Death	1	7	1
Infections			
Any	22	33	22
Severe	6	16	6

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Fever in Absence of Infection			
Any	31	41	35
Severe	2	8	2
Hypersensitivity Reactions			
Regardless of Premedication			
Any	21	20	18
Severe	4	10	3
With 3-day Premedication	n=92	n=3	n=92
Any	15	33	15
Severe	2	0	2
Fluid Retention			
Regardless of Premedication			
Any	47	39	60
Severe	7	8	9
With 3-day Premedication	n=92	n=3	n=92
Any	64	67	64
Severe	7	33	7
Neurosensory			
Any	49	34	58
Severe	4	0	6
Cutaneous			
Any	48	54	47
Severe	5	10	5
Nail Changes			
Any	31	23	41
Severe	3	5	4
Gastrointestinal			
Nausea	39	38	42
Vomiting	22	23	23
Diarrhea	39	33	43
Severe	5	5	6
Stomatitis			
Any	42	49	52
Severe	6	13	7
Alopecia	76	62	74
Asthenia			
Any	62	53	66
Severe	13	25	15
Myalgia			
Any	19	16	21
Severe	2	2	2
Arthralgia	9	7	8
Infusion Site Reactions	4	3	4

*Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN
**Elevated Baseline LFTs: AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN
***Febrile Neutropenia: ANC grade 4 with fever >38°C with intravenous antibiotics and/or hospitalization

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Hematologic Reactions
Reversible marrow suppression was the major dose-limiting toxicity of docetaxel injection concentrate *[see Warnings and Precautions (5.3)]*. The median time to nadir was 7 days, while the median duration of severe neutropenia (<500 cells/mm^3) was 7 days. Among 2045 patients with solid tumors and normal baseline LFTs, severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles.

Febrile neutropenia (<500 cells/mm^3 with fever >38°C with intravenous antibiotics and/or hospitalization) occurred in 11% of patients with solid tumors, in 12.3% of patients with metastatic breast cancer, and in 9.8% of 92 breast cancer patients premedicated with 3-day corticosteroids.

Severe infectious episodes occurred in 6.1% of patients with solid tumors, in 6.4% of patients with metastatic breast cancer, and in 5.4% of 92 breast cancer patients premedicated with 3-day corticosteroids.

Thrombocytopenia (<100,000 cells/mm^3) associated with fatal gastrointestinal hemorrhage has been reported.

Hypersensitivity Reactions
Severe hypersensitivity reactions have been reported *[see Boxed Warning, Warnings and Precautions (5.4)]*. Minor events, including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever, or chills, have been reported and resolved after discontinuing the infusion and instituting appropriate therapy.

Fluid Retention
Fluid retention can occur with the use of docetaxel injection concentrate *[see Boxed Warning, Dosage and Administration (2.6), Warnings and Precautions (5.5)]*.

Cutaneous Reactions
Severe skin toxicity is discussed elsewhere in the label *[see Warnings and Precautions (5.7)]*. Reversible cutaneous reactions characterized by a rash including localized eruptions, mainly on the feet and/or hands, but also on the arms, face, or thorax, usually associated with pruritus, have been observed. Eruptions generally occurred within 1 week after docetaxel injection concentrate infusion, recovered before the next infusion, and were not disabling.

Severe nail disorders were characterized by hypo- or hyperpigmentation, and occasionally by onycholysis (in 0.8% of patients with solid tumors) and pain.

Neurologic Reactions
Neurologic reactions are discussed elsewhere in the label *[see Warnings and Precautions (5.8)]*

Gastrointestinal Reactions
Nausea, vomiting, and diarrhea were generally mild to moderate. Severe reactions occurred in 3 to 5% of patients with solid tumors and to a similar extent among metastatic breast cancer patients. The incidence of severe reactions was 1% or less for the 92 breast cancer patients premedicated with 3-day corticosteroids.

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Severe stomatitis occurred in 5.5% of patients with solid tumors, in 7.4% of patients with metastatic breast cancer, and in 1.1% of the 92 breast cancer patients premedicated with 3-day corticosteroids.

Cardiovascular Reactions
Hypotension occurred in 2.8% of patients with solid tumors; 1.2% required treatment. Clinically meaningful events such as heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, and hypertension occurred rarely. Seven of 86 (8.1%) of metastatic breast cancer patients receiving docetaxel injection concentrate 100 mg/m^2 in a randomized trial and who had serial left ventricular ejection fractions assessed developed deterioration of LVEF by ≥10% associated with a drop below the institutional lower limit of normal.

Infusion Site Reactions
Infusion site reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, or swelling of the vein.

Hepatic Reactions
In patients with normal LFTs at baseline, bilirubin values greater than the ULN occurred in 8.9% of patients. Increases in AST or ALT >1.5 times the ULN, or alkaline phosphatase >2.5 times ULN, were observed in 18.9% and 7.3% of patients, respectively. While on docetaxel injection concentrate, increases in AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN occurred in 4.3% of patients with normal LFTs at baseline. Whether these changes were related to the drug or underlying disease has not been established.

Hematologic and Other Toxicity: Relation to dose and baseline liver chemistry abnormalities
Hematologic and other toxicity is increased at higher doses and in patients with elevated baseline liver function tests (LFTs). In the following tables, adverse drug reactions are compared for three populations: 730 patients with normal LFTs given docetaxel injection concentrate at 100 mg/m^2 in the randomized and single arm studies of metastatic breast cancer after failure of previous chemotherapy; 18 patients in these studies who had abnormal baseline LFTs (defined as AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN); and 174 patients in Japanese studies given docetaxel injection concentrate at 60 mg/m^2 who had normal LFTs (see Tables 4 and 5).

Table 4 - Hematologic Adverse Reactions in Breast Cancer Patients Previously Treated with Chemotherapy Treated at Docetaxel Injection Concentrate 100 mg/m^2 with Normal or Elevated Liver Function Tests or 60 mg/m^2 with Normal Liver Function Tests

	Docetaxel Injection Concentrate 100 mg/m^2		**Docetaxel Injection Concentrate 60 mg/m^2**
Adverse Reaction	**Normal LFTs*** **n=730** **%**	**Elevated LFTs**** **n=18** **%**	**Normal LFTs*** **n=174** **%**
Neutropenia			
Any <2000 cells/mm^3	98	100	95
Grade 4 <500 cells/mm^3	84	94	75

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Thrombocytopenia			
Any <100,000 cells/mm^3	11	44	14
Grade 4 <20,000 cells/mm^3	1	17	1
Anemia <11 g/dL	95	94	65
Infection* **			
Any	23	39	1
Grade 3 and 4	7	33	0
Febrile Neutropenia** **			
By Patient	12	33	0
By Course	2	9	0
Septic Death	2	6	1
Non-Septic Death	1	11	0

*Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

**Elevated Baseline LFTs: AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN

***Incidence of infection requiring hospitalization and/or intravenous antibiotics was 8.5% (n=62) among the 730 patients with normal LFTs at baseline; 7 patients had concurrent grade 3 neutropenia, and 46 patients had grade 4 neutropenia.

****Febrile Neutropenia: For 100 mg/m^2, ANC grade 4 and fever >38°C with intravenous antibiotics and/or hospitalization; for 60 mg/m^2, ANC grade 3/4 and fever >38.1°C

Table 5 - Non-Hematologic Adverse Reactions in Breast Cancer Patients Previously Treated with Chemotherapy Treated at Docetaxel Injection Concentrate 100 mg/m^2 with Normal or Elevated Liver Function Tests or 60 mg/m^2 with Normal Liver Function Tests

	Docetaxel Injection Concentrate 100 mg/m^2		**Docetaxel Injection Concentrate 60 mg/m^2**
Adverse Reaction	**Normal LFTs* n=730 %**	**Elevated LFTs** n=18 %**	**Normal LFTs* n=174 %**
Acute Hypersensitivity Reaction Regardless of Premedication			
Any	13	6	1
Severe	1	0	0
Fluid Retention* ** **Regardless of Premedication**			
Any	56	61	13
Severe	8	17	0
Neurosensory			
Any	57	50	20
Severe	6	0	0
Myalgia	23	33	3
Cutaneous			
Any	45	61	31
Severe	5	17	0

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Asthenia			
Any	65	44	66
Severe	17	22	0
Diarrhea			
Any	42	28	NA
Severe	6	11	
Stomatitis			
Any	53	67	19
Severe	8	39	1

*Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN
** Elevated Baseline Liver Function: AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN
***Fluid Retention includes (by COSTART): edema (peripheral, localized, generalized, lymphedema, pulmonary edema, and edema otherwise not specified) and effusion (pleural, pericardial, and ascites); no premedication given with the 60 mg/m^2 dose
NA = not available

In the three-arm monotherapy trial, TAX313, which compared docetaxel injection concentrate 60 mg/m^2, 75 mg/m^2 and 100 mg/m^2 in advanced breast cancer, grade 3/4 or severe adverse reactions occurred in 49.0% of patients treated with docetaxel injection concentrate 60 mg/m^2 compared to 55.3% and 65.9% treated with 75 mg/m^2 and 100 mg/m^2 respectively. Discontinuation due to adverse reactions was reported in 5.3% of patients treated with 60 mg/m^2 vs. 6.9% and 16.5% for patients treated at 75 and 100 mg/m^2 respectively. Deaths within 30 days of last treatment occurred in 4.0% of patients treated with 60 mg/m^2 compared to 5.3% and 1.6% for patients treated at 75 mg/m^2 and 100 mg/m^2 respectively.

The following adverse reactions were associated with increasing docetaxel doses: fluid retention (26%, 38%, and 46% at 60 mg/m^2, 75 mg/m^2, and 100 mg/m^2 respectively), thrombocytopenia (7%, 11% and 12% respectively), neutropenia (92%, 94%, and 97% respectively), febrile neutropenia (5%, 7%, and 14% respectively), treatment-related grade 3/4 infection (2%, 3%, and 7% respectively) and anemia (87%, 94%, and 97% respectively).

Combination therapy with docetaxel injection concentrate in the adjuvant treatment of breast cancer
The following table presents treatment emergent adverse reactions observed in 744 patients, who were treated with docetaxel injection concentrate 75 mg/m^2 every 3 weeks in combination with doxorubicin and cyclophosphamide (see Table 6).

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Table 6- Clinically Important Treatment Emergent Adverse Reactions Regardless of Causal Relationship in Patients Receiving Docetaxel Injection Concentrate in Combination with Doxorubicin and Cyclophosphamide (TAX316).

	Docetaxel Injection Concentrate 75 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (TAC) n=744 %		**Fluorouracil 500 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m^2 (FAC) n=736 %**	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Anemia	92	4	72	2
Neutropenia	71	66	82	49
Fever in absence of infection	47	1	17	0
Infection	39	4	36	2
Thrombocytopenia	39	2	28	1
Febrile neutropenia	25	N/A	3	N/A
Neutropenic infection	12	N/A	6	N/A
Hypersensitivity reactions	13	1	4	0
Lymphedema	4	0	1	0
Fluid Retention*	35	1	15	0
Peripheral edema	27	0	7	0
Weight gain	13	0	9	0
Neuropathy sensory	26	0	10	0
Neuro-cortical	5	1	6	1
Neuropathy motor	4	0	2	0
Neuro-cerebellar	2	0	2	0
Syncope	2	1	1	0
Alopecia	98	N/A	97	N/A
Skin toxicity	27	1	18	0
Nail disorders	19	0	14	0
Nausea	81	5	88	10
Stomatitis	69	7	53	2
Vomiting	45	4	59	7
Diarrhea	35	4	28	2
Constipation	34	1	32	1
Taste perversion	28	1	15	0
Anorexia	22	2	18	1
Abdominal Pain	11	1	5	0
Amenorrhea	62	N/A	52	N/A
Cough	14	0	10	0
Cardiac dysrhythmias	8	0	6	0
Vasodilatation	27	1	21	1

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Hypotension	2	0	1	0
Phlebitis	1	0	1	0
Asthenia	81	11	71	6
Myalgia	27	1	10	0
Arthralgia	19	1	9	0
Lacrimation disorder	11	0	7	0
Conjunctivitis	5	0	7	0

* COSTART term and grading system for events related to treatment.

Of the 744 patients treated with TAC, 36.3% experienced severe treatment emergent adverse reactions compared to 26.6% of the 736 patients treated with FAC. Dose reductions due to hematologic toxicity occurred in 1% of cycles in the TAC arm versus 0.1% of cycles in the FAC arm. Six percent of patients treated with TAC discontinued treatment due to adverse reactions, compared to 1.1% treated with FAC; fever in the absence of infection and allergy being the most common reasons for withdrawal among TAC-treated patients. Two patients died in each arm within 30 days of their last study treatment; 1 death per arm was attributed to study drugs.

Fever and Infection
Fever in the absence of infection was seen in 46.5% of TAC-treated patients and in 17.1% of FAC-treated patients. Grade 3/4 fever in the absence of infection was seen in 1.3% and 0% of TAC- and FAC-treated patients respectively. Infection was seen in 39.4% of TAC-treated patients compared to 36.3% of FAC-treated patients. Grade 3/4 infection was seen in 3.9% and 2.2% of TAC-treated and FAC-treated patients respectively. There were no septic deaths in either treatment arm.

Gastrointestinal Reactions
In addition to gastrointestinal reactions reflected in the table above, 7 patients in the TAC arm were reported to have colitis/enteritis/large intestine perforation vs. one patient in the FAC arm. Five of the 7 TAC-treated patients required treatment discontinuation; no deaths due to these events occurred.

Cardiovascular Reactions
More cardiovascular reactions were reported in the TAC arm vs. the FAC arm; dysrhythmias, all grades (7.9% vs. 6.0%), hypotension, all grades (2.6% vs. 1.1%) and CHF (2.3% vs. 0.9%, at 70 months median follow-up). One patient in each arm died due to heart failure.

Acute Myeloid Leukemia (AML)
Treatment-related acute myeloid leukemia or myelodysplasia is known to occur in patients treated with anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. AML occurs at a higher frequency when these agents are given in combination with radiation therapy. AML occurred in the adjuvant breast cancer trial (TAX316). The cumulative risk of developing treatment-related AML at 5 years in TAX316 was 0.4% for TAC-treated patients and 0.1% for FAC-treated patients. This risk of AML is comparable to the risk observed for other anthracyclines/cyclophosphamide containing adjuvant breast chemotherapy regimens.

<u>Lung Cancer</u>
Monotherapy with Docetaxel injection concentrate for unresectable, locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy

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Docetaxel injection concentrate 75 mg/m^2: Treatment emergent adverse drug reactions are shown in Table 7. Included in this table are safety data for a total of 176 patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who were treated in two randomized, controlled trials. These reactions were described using NCI Common Toxicity Criteria regardless of relationship to study treatment, except for the hematologic toxicities or where otherwise noted.

Table 7 - Treatment Emergent Adverse Reactions Regardless of Relationship to Treatment in Patients Receiving Docetaxel Injection Concentrate as Monotherapy for Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy*

Adverse Reaction	**Docetaxel Injection Concentrate 75 mg/m^2 n=176 %**	**Best Supportive Care n=49 %**	**Vinorelbine/ Ifosfamide n=119 %**
Neutropenia			
Any	84	14	83
Grade 3/4	65	12	57
Leukopenia			
Any	84	6	89
Grade 3/4	49	0	43
Thrombocytopenia			
Any	8	0	8
Grade 3/4	3	0	2
Anemia			
Any	91	55	91
Grade 3/4	9	12	14
Febrile Neutropenia**	6	NA†	1
Infection			
Any	34	29	30
Grade 3/4	10	6	9
Treatment Related Mortality	3	NA†	3
Hypersensitivity Reactions			
Any	6	0	1
Grade 3/4	3	0	0
Fluid Retention			
Any	34	ND††	23
Severe	3		3
Neurosensory			
Any	23	14	29
Grade 3/4	2	6	5
Neuromotor			

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Any	16	8	10
Grade 3/4	5	6	3
Skin			
Any	20	6	17
Grade 3/4	1	2	1
Gastrointestinal			
Nausea			
Any	34	31	31
Grade 3/4	5	4	8
Vomiting			
Any	22	27	22
Grade 3/4	3	2	6
Diarrhea			
Any	23	6	12
Grade 3/4	3	0	4
Alopecia	56	35	50
Asthenia			
Any	53	57	54
Severe***	18	39	23
Stomatitis			
Any	26	6	8
Grade 3/4	2	0	1
Pulmonary			
Any	41	49	45
Grade 3/4	21	29	19
Nail Disorder			
Any	11	0	2
Severe***	1	0	0
Myalgia			
Any	6	0	3
Severe***	0	0	0
Arthralgia			
Any	3	2	2
Severe***	0	0	1
Taste Perversion			
Any	6	0	0
Severe***	1	0	0

*Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN
**Febrile Neutropenia: ANC grade 4 with fever >38°C with intravenous antibiotics and/or hospitalization
***COSTART term and grading system
†Not Applicable; †† Not Done

Combination therapy with Docetaxel injection concentrate in chemotherapy-naïve advanced unresectable or metastatic NSCLC

Table 8 presents safety data from two arms of an open label, randomized controlled trial (TAX326) that enrolled patients with unresectable stage IIIB or IV non-small cell lung cancer and no history of prior

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chemotherapy. Adverse reactions were described using the NCI Common Toxicity Criteria except where otherwise noted.

Table 8 - Adverse Reactions Regardless of Relationship to Treatment in Chemotherapy-Naïve Advanced Non-Small Cell Lung Cancer Patients Receiving Docetaxel Injection Concentrate in Combination with Cisplatin

Adverse Reaction	**Docetaxel Injection Concentrate 75 mg/m^2 + Cisplatin 75 mg/m^2 n=406 %**	**Vinorelbine 25 mg/m^2 + Cisplatin 100 mg/m^2 n=396 %**
Neutropenia		
Any	91	90
Grade 3/4	74	78
Febrile Neutropenia	5	5
Thrombocytopenia		
Any	15	15
Grade 3/4	3	4
Anemia		
Any	89	94
Grade 3/4	7	25
Infection		
Any	35	37
Grade 3/4	8	8
Fever in absence of infection		
Any	33	29
Grade 3/4	< 1	1
Hypersensitivity Reaction*		
Any	12	4
Grade 3/4	3	< 1
Fluid Retention**		
Any	54	42
All severe or life-threatening events	2	2
Pleural effusion		
Any	23	22
All severe or life-threatening events	2	2
Peripheral edema		
Any	34	18
All severe or life-threatening events	<1	<1
Weight gain		
Any	15	9
All severe or life-threatening events	<1	<1
Neurosensory		
Any	47	42
Grade 3/4	4	4

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Neuromotor		
Any	19	17
Grade 3/4	3	6
Skin		
Any	16	14
Grade 3/4	<1	1
Nausea		
Any	72	76
Grade 3/4	10	17
Vomiting		
Any	55	61
Grade 3/4	8	16
Diarrhea		
Any	47	25
Grade 3/4	7	3
Anorexia**		
Any	42	40
All severe or life-threatening events	5	5
Stomatitis		
Any	24	21
Grade 3/4	2	1
Alopecia		
Any	75	42
Grade 3	<1	0
Asthenia**		
Any	74	75
All severe or life-threatening events	12	14
Nail Disorder**		
Any	14	<1
All severe events	<1	0
Myalgia**		
Any	18	12
All severe events	<1	<1

* Replaces NCI term “Allergy”
** COSTART term and grading system

Deaths within 30 days of last study treatment occurred in 31 patients (7.6%) in the docetaxel+cisplatin arm and 37 patients (9.3%) in the vinorelbine+cisplatin arm. Deaths within 30 days of last study treatment attributed to study drug occurred in 9 patients (2.2%) in the docetaxel+cisplatin arm and 8 patients (2.0%) in the vinorelbine+cisplatin arm.

The second comparison in the study, vinorelbine+cisplatin versus docetaxel injection concentrate+carboplatin (which did not demonstrate a superior survival associated with docetaxel injection concentrate, *[see Clinical Studies (14.3)]*) demonstrated a higher incidence of thrombocytopenia, diarrhea, fluid retention, hypersensitivity reactions, skin toxicity, alopecia and nail changes on the docetaxel injection concentrate+carboplatin arm, while a higher incidence of anemia,

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neurosensory toxicity, nausea, vomiting, anorexia and asthenia was observed on the vinorelbine+cisplatin arm.

Prostate Cancer

Combination therapy with Docetaxel injection concentrate in patients with prostate cancer

The following data are based on the experience of 332 patients, who were treated with docetaxel injection concentrate 75 mg/m² every 3 weeks in combination with prednisone 5 mg orally twice daily (see Table 9).

Table 9 - Clinically Important Treatment Emergent Adverse Reactions (Regardless of Relationship) in Patients with Prostate Cancer who Received Docetaxel Injection Concentrate in Combination with Prednisone (TAX327)

	Docetaxel Injection Concentrate 75 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=332 %		**Mitoxantrone 12 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=335 %**	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Anemia	67	5	58	2
Neutropenia	41	32	48	22
Thrombocytopenia	3	1	8	1
Febrile neutropenia	3	N/A	2	N/A
Infection	32	6	20	4
Epistaxis	6	0	2	0
Allergic Reactions	8	1	1	0
Fluid Retention*	24	1	5	0
Weight Gain*	8	0	3	0
Peripheral Edema*	18	0	2	0
Neuropathy Sensory	30	2	7	0
Neuropathy Motor	7	2	3	1
Rash/Desquamation	6	0	3	1
Alopecia	65	N/A	13	N/A
Nail Changes	30	0	8	0
Nausea	41	3	36	2
Diarrhea	32	2	10	1
Stomatitis/Pharyngitis	20	1	8	0
Taste Disturbance	18	0	7	0
Vomiting	17	2	14	2
Anorexia	17	1	14	0
Cough	12	0	8	0
Dyspnea	15	3	9	1
Cardiac left ventricular function	10	0	22	1
Fatigue	53	5	35	5
Myalgia	15	0	13	1

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Tearing	10	1	2	0
Arthralgia	8	1	5	1

*Related to treatment

Gastric Cancer

Combination therapy with Docetaxel injection concentrate in gastric adenocarcinoma

Data in the following table are based on the experience of 221 patients with advanced gastric adenocarcinoma and no history of prior chemotherapy for advanced disease, who were treated with docetaxel injection concentrate 75 mg/m^2 in combination with cisplatin and fluorouracil (see Table 10).

Table 10 - Clinically Important Treatment Emergent Adverse Reactions Regardless of Relationship to Treatment in the Gastric Cancer Study

	Docetaxel Injection Concentrate 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 n=221		**Cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 n=224**	
Adverse Reaction	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**
Anemia	97	18	93	26
Neutropenia	96	82	83	57
Fever in the absence of infection	36	2	23	1
Thrombocytopenia	26	8	39	14
Infection	29	16	23	10
Febrile neutropenia	16	N/A	5	N/A
Neutropenic infection	16	N/A	10	N/A
Allergic reactions	10	2	6	0
Fluid retention*	15	0	4	0
Edema*	13	0	3	0
Lethargy	63	21	58	18
Neurosensory	38	8	25	3
Neuromotor	9	3	8	3
Dizziness	16	5	8	2
Alopecia	67	5	41	1
Rash/itch	12	1	9	0
Nail changes	8	0	0	0
Skin desquamation	2	0	0	0
Nausea	73	16	76	19
Vomiting	67	15	73	19
Anorexia	51	13	54	12
Stomatitis	59	21	61	27
Diarrhea	78	20	50	8
Constipation	25	2	34	3
Esophagitis/dysphagia/odynophagia	16	2	14	5
Gastrointestinal pain/cramping	11	2	7	3

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Cardiac dysrhythmias	5	2	2	1
Myocardial ischemia	1	0	3	2
Tearing	8	0	2	0
Altered hearing	6	0	13	2

Clinically important treatment emergent adverse reactions were determined based upon frequency, severity, and clinical impact of the adverse reaction.
*Related to treatment

Head and Neck Cancer

Combination therapy with Docetaxel injection concentrate in head and neck cancer

Table 11 summarizes the safety data obtained from patients that received induction chemotherapy with Docetaxel Injection Concentrate 75 mg/m^2 in combination with cisplatin and fluorouracil followed by radiotherapy (TAX323; 174 patients) or chemoradiotherapy (TAX324; 251 patients). The treatment regimens are described in Section 14.6.

Table 11 – Clinically Important Treatment Emergent Adverse Reactions (Regardless of Relationship) in Patients with SCCHN Receiving Induction Chemotherapy with Docetaxel Injection Concentrate in Combination with Cisplatin and Fluorouracil Followed by Radiotherapy (TAX323) or Chemoradiotherapy (TAX324)

	TAX323 (n=355)				**TAX324 (n=494)**			
	Docetaxel Injection Concentrate arm (n=174)		**Comparator arm (n=181)**		**Docetaxel Injection Concentrate arm (n=251)**		**Comparator arm (n=243)**	
Adverse Reaction (by Body System)	**Any** %	**Grade** 3/4 %	**Any** %	**Grade** 3/4 %	**Any** %	**Grade** 3/4 %	**Any** %	**Grade** 3/4 %
Neutropenia	93	76	87	53	95	84	84	56
Anemia	89	9	88	14	90	12	86	10
Thrombocytopenia	24	5	47	18	28	4	31	11
Infection	27	9	26	8	23	6	28	5
Febrile neutropenia*	5	N/A	2	N/A	12	N/A	7	N/A
Neutropenic infection	14	N/A	8	N/A	12	N/A	8	N/A
Cancer pain	21	5	16	3	17	9	20	11
Lethargy	41	3	38	3	61	5	56	10
Fever in the absence of infection	32	1	37	0	30	4	28	3
Myalgia	10	1	7	0	7	0	7	2
Weight loss	21	1	27	1	14	2	14	2
Allergy	6	0	3	0	2	0	0	0
Fluid retention**	20	0	14	1	13	1	7	2
Edema only	13	0	7	0	12	1	6	1
Weight gain only	6	0	6	0	0	0	1	0
Dizziness	2	0	5	1	16	4	15	2

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Neurosensory	18	1	11	1	14	1	14	0
Altered hearing	6	0	10	3	13	1	19	3
Neuromotor	2	1	4	1	9	0	10	2
Alopecia	81	11	43	0	68	4	44	1
Rash/itch	12	0	6	0	20	0	16	1
Dry skin	6	0	2	0	5	0	3	0
Desquamation	4	1	6	0	2	0	5	0
Nausea	47	1	51	7	77	14	80	14
Stomatitis	43	4	47	11	66	21	68	27
Vomiting	26	1	39	5	56	8	63	10
Diarrhea	33	3	24	4	48	7	40	3
Constipation	17	1	16	1	27	1	38	1
Anorexia	16	1	25	3	40	12	34	12
Esophagitis/dysphagia/ Odynophagia	13	1	18	3	25	13	26	10
Taste, sense of smell altered	10	0	5	0	20	0	17	1
Gastrointestinal pain/cramping	8	1	9	1	15	5	10	2
Heartburn	6	0	6	0	13	2	13	1
Gastrointestinal bleeding	4	2	0	0	5	1	2	1
Cardiac dysrhythmia	2	2	2	1	6	3	5	3
Venous* **	3	2	6	2	4	2	5	4
Ischemia myocardial	2	2	1	0	2	1	1	1
Tearing	2	0	1	0	2	0	2	0
Conjunctivitis	1	0	1	0	1	0	0.4	0

Clinically important treatment emergent adverse reactions based upon frequency, severity, and clinical impact.
*Febrile neutropenia: grade ≥2 fever concomitant with grade 4 neutropenia requiring intravenous antibiotics and/or hospitalization.
**Related to treatment.
*** Includes superficial and deep vein thrombosis and pulmonary embolism

6.2 Post-Marketing Experiences

The following adverse reactions have been identified from clinical trials and/or post-marketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.

Body as a whole: diffuse pain, chest pain, radiation recall phenomenon.

Cardiovascular: atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction.

Cutaneous: very rare cases of cutaneous lupus erythematosus and rare cases of bullous eruptions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and Scleroderma-like changes usually preceded by peripheral lymphedema. In some cases multiple factors may have contributed to the development of these effects. Severe hand and foot syndrome has been reported.

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Gastrointestinal: abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, ischemic colitis, colitis, intestinal obstruction, ileus, neutropenic enterocolitis and dehydration as a consequence to gastrointestinal events have been reported.

Hematologic: bleeding episodes. Disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure, has been reported. Cases of acute myeloid leukemia and myelodysplasic syndrome have been reported in association with docetaxel injection concentrate when used in combination with other chemotherapy agents and/or radiotherapy.

Hypersensitivity: rare cases of anaphylactic shock have been reported. Very rarely these cases resulted in a fatal outcome in patients who received premedication.

Hepatic: rare cases of hepatitis, sometimes fatal primarily in patients with pre-existing liver disorders, have been reported.

Neurologic: confusion, rare cases of seizures or transient loss of consciousness have been observed, sometimes appearing during the infusion of the drug.

Ophthalmologic: conjunctivitis, lacrimation or lacrimation with or without conjunctivitis. Excessive tearing which may be attributable to lacrimal duct obstruction has been reported. Rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during drug infusion and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion.

Hearing: rare cases of ototoxicity, hearing disorders and/or hearing loss have been reported, including cases associated with other ototoxic drugs.

Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome, interstitial pneumonia. Pulmonary fibrosis has been rarely reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

Renal: renal insufficiency and renal failure have been reported, the majority of these cases were associated with concomitant nephrotoxic drugs.

7. DRUG INTERACTIONS

Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of Docetaxel Injection Concentrate and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with Docetaxel Injection Concentrate, close monitoring for toxicity and a Docetaxel Injection

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Concentrate dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see 'Warnings and Precautions' section]*
Based on its mechanism of action and findings in animals, docetaxel injection concentrate can cause fetal harm when administered to a pregnant woman. If docetaxel injection concentrate is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with docetaxel injection concentrate.

Docetaxel injection concentrate can cause fetal harm when administered to a pregnant woman. Studies in both rats and rabbits at doses ≥0.3 and 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m^2 basis), administered during the period of organogenesis, have shown that docetaxel injection concentrate is embryotoxic and fetotoxic (characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay). The doses indicated above also caused maternal toxicity.

8.3 Nursing Mothers

It is not known whether docetaxel is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from docetaxel injection concentrate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of docetaxel injection concentrate in pediatric patients have not been established.

8.5 Geriatric Use

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

Non-Small Cell Lung Cancer
In a study conducted in chemotherapy-naïve patients with NSCLC (TAX326), 148 patients (36%) in the docetaxel injection concentrate+cisplatin group were 65 years of age or greater. There were 128 patients (32%) in the vinorelbine+cisplatin group 65 years of age or greater. In the docetaxel injection concentrate+cisplatin group, patients less than 65 years of age had a median survival of 10.3 months (95% CI: 9.1 months, 11.8 months) and patients 65 years or older had a median survival of 12.1 months (95% CI: 9.3 months, 14 months). In patients 65 years of age or greater treated with docetaxel injection concentrate+cisplatin, diarrhea (55%), peripheral edema (39%) and stomatitis (28%) were observed more frequently than in the vinorelbine+cisplatin group (diarrhea 24%, peripheral edema 20%, stomatitis 20%). Patients treated with docetaxel injection concentrate+cisplatin who were 65 years of age or greater were more likely to experience diarrhea (55%), infections (42%), peripheral edema (39%)

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and stomatitis (28%) compared to patients less than the age of 65 administered the same treatment (43%, 31%, 31% and 21%, respectively).

When docetaxel injection concentrate was combined with carboplatin for the treatment of chemotherapy-naïve, advanced non-small cell lung carcinoma, patients 65 years of age or greater (28%) experienced higher frequency of infection compared to similar patients treated with docetaxel injection concentrate+cisplatin, and a higher frequency of diarrhea, infection and peripheral edema than elderly patients treated with vinorelbine+cisplatin.

Prostate Cancer
Of the 333 patients treated with docetaxel injection concentrate every three weeks plus prednisone in the prostate cancer study (TAX327), 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with docetaxel injection concentrate every three weeks, the following treatment emergent adverse reactions occurred at rates ≥10% higher in patients 65 years of age or greater compared to younger patients: anemia (71% vs. 59%), infection (37% vs. 24%), nail changes (34% vs. 23%), anorexia (21% vs. 10%), weight loss (15% vs. 5%) respectively.

Breast Cancer
In the adjuvant breast cancer trial (TAX316), docetaxel injection concentrate in combination with doxorubicin and cyclophosphamide was administered to 744 patients of whom 48 (6%) were 65 years of age or greater. The number of elderly patients who received this regimen was not sufficient to determine whether there were differences in safety and efficacy between elderly and younger patients.

Gastric Cancer
Among the 221 patients treated with docetaxel injection concentrate in combination with cisplatin and fluorouracil in the gastric cancer study, 54 were 65 years of age or older and 2 patients were older than 75 years. In this study, the number of patients who were 65 years of age or older was insufficient to determine whether they respond differently from younger patients. However, the incidence of serious adverse reactions was higher in the elderly patients compared to younger patients. The incidence of the following adverse reactions (all grades, regardless of relationship): lethargy, stomatitis, diarrhea, dizziness, edema, febrile neutropenia/neutropenic infection occurred at rates ≥10% higher in patients who were 65 years of age or older compared to younger patients. Elderly patients treated with TCF should be closely monitored.

Head and Neck Cancer
Among the 174 and 251 patients who received the induction treatment with docetaxel injection concentrate in combination with cisplatin and fluorouracil (TPF) for SCCHN in the TAX323 and TAX324 studies, 18 (10%) and 32 (13%) of the patients were 65 years of age or older, respectively.

These clinical studies of docetaxel injection concentrate in combination with cisplatin and fluorouracil in patients with SCCHN did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience with this treatment regimen has not identified differences in responses between elderly and younger patients.

8.6 Hepatic Impairment

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Patients with bilirubin >ULN should not receive Docetaxel Injection Concentrate. Also, patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN should not receive Docetaxel Injection Concentrate *[see Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

10. OVERDOSAGE

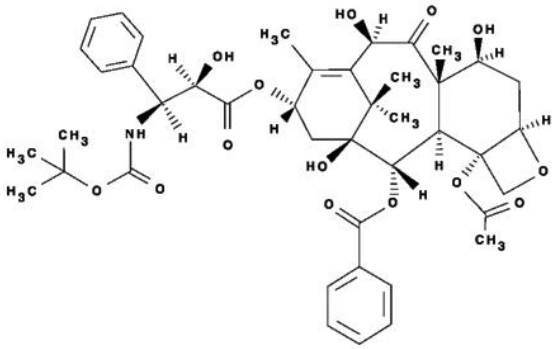
There is no known antidote for docetaxel injection concentrate overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

In two reports of overdose, one patient received 150 mg/m^2 and the other received 200 mg/m^2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.

In mice, lethality was observed following single intravenous doses that were ≥154 mg/kg (about 4.5 times the human dose of 100 mg/m^2 on a mg/m^2 basis); neurotoxicity associated with paralysis, non-extension of hind limbs, and myelin degeneration was observed in mice at 48 mg/kg (about 1.5 times the human dose of 100 mg/m^2 basis). In male and female rats, lethality was observed at a dose of 20 mg/kg (comparable to the human dose of 100 mg/m^2 on a mg/m^2 basis) and was associated with abnormal mitosis and necrosis of multiple organs.

11. DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, anhydrous. Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}$, and a molecular weight of 807.88. It is highly lipophilic and practically insoluble in water.

<u>One-vial Docetaxel Injection Concentrate</u>

Docetaxel injection concentrate is a sterile, non-pyrogenic, clear, viscous, colorless to pale yellow solution, without macroscopic particles in solution at 20 mg/mL docetaxel concentration.

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Each mL contains 20 mg docetaxel, citric acid anhydrous (6 mg), kollidon 12 PF (povidone P12) (100 mg), polysorbate 80 (424 mg) and ethanol (400 mg/ mL).

Docetaxel injection concentrate is available in single use vials containing 20 mg (1 mL), 80 mg (4 mL) or 140 mg (7 mL) docetaxel.

Docetaxel injection concentrate requires NO prior dilution with a diluent and is ready to add to the infusion solution.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

12.3 Human Pharmacokinetics

Absorption: The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m^2 to 115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m^2.

Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. *In vitro* studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

Metabolism: *In vitro* drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4 *[see Drug Interactions (7)]*.

Elimination: A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

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Effect of Age: A population pharmacokinetic analysis was carried out after docetaxel treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age.

Effect of Gender: The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel.

Hepatic Impairment: The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should not be treated with Docetaxel Injection Concentrate. Patients with severe hepatic impairment have not been studied *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.

Effect of Race: Mean total body clearance for Japanese patients dosed at the range of 10 mg/m^2 to 90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.

Effect of Ketoconazole: The effect of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of docetaxel was investigated in 7 cancer patients. Patients were randomized to receive either docetaxel (100 mg/m^2 intravenous) alone or docetaxel (10 mg/m^2 intravenous) in combination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was co-administered with ketoconazole *[see Dosage and Administration (2.7) and Drug Interactions (7)]*.

Effect of Combination Therapies:

- **Dexamethasone:** Docetaxel total body clearance was not modified by pretreatment with dexamethasone.

- **Cisplatin:** Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.

- **Cisplatin and Fluorouracil:** The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug.

- **Prednisone:** A population pharmacokinetic analysis of plasma data from 40 patients with hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone.

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- **Cyclophosphamide and Doxorubicin:** A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with docetaxel have not been performed.

Docetaxel was clastogenic in the *in vitro* chromosome aberration test in CHO-K_1 cells and in the *in vivo* micronucleus test in mice administered doses of 0.39 to 1.56 mg/kg (about $1/60^{th}$ to $1/15^{th}$ the recommended human dose on a mg/m^2 basis). Docetaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assays.

Docetaxel did not reduce fertility in rats when administered in multiple intravenous doses of up to 0.3 mg/kg (about $1/50^{th}$ the recommended human dose on a mg/m^2 basis), but decreased testicular weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at intravenous doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about $1/3^{rd}$ and $1/15^{th}$ the recommended human dose on a mg/m^2 basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

14. CLINICAL STUDIES

14.1 Locally Advanced or Metastatic Breast Cancer

The efficacy and safety of docetaxel injection concentrate have been evaluated in locally advanced or metastatic breast cancer after failure of previous chemotherapy (alkylating agent-containing regimens or anthracycline-containing regimens).

<u>Randomized Trials</u>

In one randomized trial, patients with a history of prior treatment with an anthracycline-containing regimen were assigned to treatment with docetaxel injection concentrate (100 mg/m^2 every 3 weeks) or the combination of mitomycin (12 mg/m^2 every 6 weeks) and vinblastine (6 mg/m^2 every 3 weeks). Two hundred three patients were randomized to docetaxel injection concentrate and 189 to the comparator arm. Most patients had received prior chemotherapy for metastatic disease; only 27 patients on the docetaxel injection concentrate arm and 33 patients on the comparator arm entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The following table summarizes the study results (See Table 12).

Reference ID: 3400944

Table 12 - Efficacy of Docetaxel Injection Concentrate in the Treatment of Breast Cancer Patients Previously Treated with an Anthracycline-Containing Regimen (Intent-to-Treat Analysis)

Efficacy Parameter	Docetaxel (n=203)	Mitomycin/ Vinblastine (n=189)	p-value
Median Survival	11.4 months	8.7 months	p=0.01 Log Rank
Risk Ratio*, Mortality (Docetaxel: Control)	0.73		
95% CI (Risk Ratio)	0.58 to 0.93		
Median Time to Progression	4.3 months	2.5 months	
Risk Ratio*, Progression (Docetaxel: Control)	0.75		p=0.01 Log Rank
95% CI (Risk Ratio)	0.61 to 0.94		
Overall Response Rate Complete Response Rate	28.1% 3.4%	9.5% 1.6%	p<0.0001 Chi Square

*For the risk ratio, a value less than 1.00 favors docetaxel.

In a second randomized trial, patients previously treated with an alkylating-containing regimen were assigned to treatment with docetaxel injection concentrate (100 mg/m^2) or doxorubicin (75 mg/m^2) every 3 weeks. One hundred sixty-one patients were randomized to docetaxel injection concentrate and 165 patients to doxorubicin. Approximately one-half of patients had received prior chemotherapy for metastatic disease, and one-half entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The study results are summarized below (See Table 13).

Table 13 - Efficacy of Docetaxel Injection Concentrate in the Treatment of Breast Cancer Patients Previously Treated with an Alkylating-Containing Regimen (Intent-to-Treat Analysis)

Efficacy Parameter	Docetaxel (n=161)	Doxorubicin (n=165)	p-value
Median Survival	14.7 months	14.3 months	p=0.39 Log Rank
Risk Ratio*, Mortality (Docetaxel: Control)	0.89		
95% CI (Risk Ratio)	0.68 to 1.16		
Median Time to Progression	6.5 months	5.3 months	
Risk Ratio*, Progression (Docetaxel: Control)	0.93		p=0.45 Log Rank

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95% CI (Risk Ratio)	0.71 to 1.16		
Overall Response Rate Complete Response Rate	45.3% 6.8%	29.7% 4.2%	p=0.004 Chi Square

*For the risk ratio, a value less than 1.00 favors docetaxel.

In another multicenter open-label, randomized trial (TAX313), in the treatment of patients with advanced breast cancer who progressed or relapsed after one prior chemotherapy regimen, 527 patients were randomized to receive docetaxel injection concentrate monotherapy 60 mg/m^2 (n=151), 75 mg/m^2 (n=188) or 100 mg/m^2 (n=188). In this trial, 94% of patients had metastatic disease and 79% had received prior anthracycline therapy. Response rate was the primary endpoint.

Response rates increased with docetaxel injection concentrate dose: 19.9% for the 60 mg/m^2 group compared to 22.3% for the 75 mg/m^2 and 29.8% for the 100 mg/m^2 group; pair-wise comparison between the 60 mg/m^2 and 100 mg/m^2 groups was statistically significant (p=0.037).

Single Arm Studies

Docetaxel injection concentrate at a dose of 100 mg/m^2 was studied in six single arm studies involving a total of 309 patients with metastatic breast cancer in whom previous chemotherapy had failed. Among these, 190 patients had anthracycline-resistant breast cancer, defined as progression during an anthracycline-containing chemotherapy regimen for metastatic disease, or relapse during an anthracycline-containing adjuvant regimen. In anthracycline-resistant patients, the overall response rate was 37.9% (72/190; 95% C.I.: 31.0 to 44.8) and the complete response rate was 2.1%.

Docetaxel injection concentrate was also studied in three single arm Japanese studies at a dose of 60 mg/m^2, in 174 patients who had received prior chemotherapy for locally advanced or metastatic breast cancer. Among 26 patients whose best response to an anthracycline had been progression, the response rate was 34.6% (95% C.I.: 17.2 to 55.7), similar to the response rate in single arm studies of 100 mg/m^2.

14.2 Adjuvant Treatment of Breast Cancer

A multicenter, open-label, randomized trial (TAX316) evaluated the efficacy and safety of docetaxel injection concentrate for the adjuvant treatment of patients with axillary-node-positive breast cancer and no evidence of distant metastatic disease. After stratification according to the number of positive lymph nodes (1 to 3, 4+), 1491 patients were randomized to receive either docetaxel injection concentrate 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAC arm), or doxorubicin 50 mg/m^2 followed by fluorouracil 500 mg/m^2 and cyclosphosphamide 500 mg/m^2 (FAC arm). Both regimens were administered every 3 weeks for 6 cycles. Docetaxel injection concentrate was administered as a 1-hour infusion; all other drugs were given as intravenous bolus on day 1. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 5 years. Adjuvant radiation therapy was prescribed according to guidelines in place at participating institutions and was given to 69% of patients who received TAC and 72% of patients who received FAC.

Results from a second interim analysis (median follow-up 55 months) are as follows: In study TAX316, the docetaxel-containing combination regimen TAC showed significantly longer disease-free survival (DFS) than FAC (hazard ratio=0.74; 2-sided 95% CI=0.60, 0.92, stratified log rank p=0.0047). The primary endpoint, disease-free survival, included local and distant recurrences, contralateral breast

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cancer and deaths from any cause. The overall reduction in risk of relapse was 25.7% for TAC-treated patients. (See Figure 1).

At the time of this interim analysis, based on 219 deaths, overall survival was longer for TAC than FAC (hazard ratio=0.69, 2-sided 95% CI=0.53, 0.90). (See Figure 2). There will be further analysis at the time survival data mature.

Figure 1 - TAX316 Disease Free Survival K-M curve

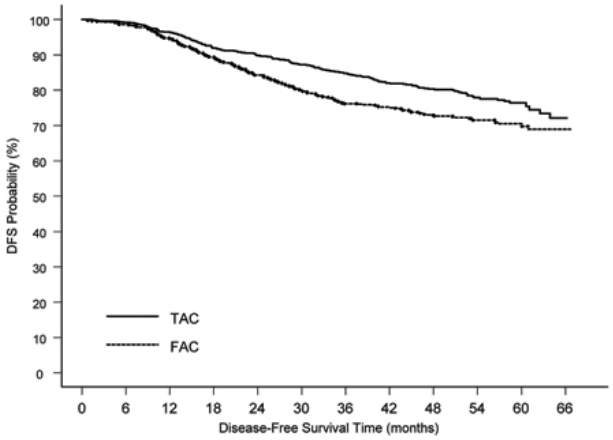
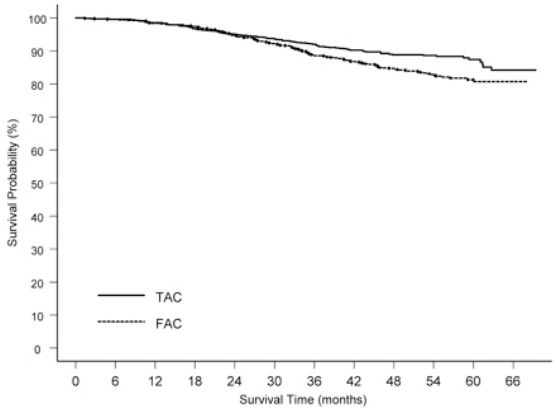


Figure 2 - TAX316 Overall Survival K-M Curve



The following table describes the results of subgroup analyses for DFS and OS (See Table 14).

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Table 14 - Subset Analyses-Adjuvant Breast Cancer Study

		Disease Free Survival		Overall Survival	
Patient subset	**Number of patients**	**Hazard ratio***	**95% CI**	**Hazard ratio***	**95% CI**
No. of positive nodes					
Overall	744	0.74	(0.60, 0.92)	0.69	(0.53, 0.90)
1 to 3	467	0.64	(0.47, 0.87)	0.45	(0.29, 0.70)
4+	277	0.84	(0.63, 1.12)	0.93	(0.66, 1.32)
Receptor status					
Positive	566	0.76	(0.59, 0.98)	0.69	(0.48, 0.99)
Negative	178	0.68	(0.48, 0.97)	0.66	(0.44, 0.98)

*a hazard ratio of less than 1 indicates that TAC is associated with a longer disease free survival or overall survival compared to FAC.

14.3 Non-Small Cell Lung Cancer (NSCLC)

The efficacy and safety of docetaxel injection concentrate has been evaluated in patients with unresectable, locally advanced or metastatic non-small cell lung cancer whose disease has failed prior platinum-based chemotherapy or in patients who are chemotherapy-naïve.

Monotherapy with Docetaxel Injection Concentrate for NSCLC Previously Treated with Platinum-Based Chemotherapy

Two randomized, controlled trials established that a docetaxel injection concentrate dose of 75 mg/m^2 was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy (see below). Docetaxel injection concentrate at a dose of 100 mg/m^2, however, was associated with unacceptable hematologic toxicity, infections, and treatment-related mortality and this dose should not be used *[see Boxed Warning, Dosage and Administration (2.7), Warnings and Precautions (5.3)]*.

One trial (TAX317), randomized patients with locally advanced or metastatic non-small cell lung cancer, a history of prior platinum-based chemotherapy, no history of taxane exposure, and an ECOG performance status ≤2 to docetaxel injection concentrate or best supportive care. The primary endpoint of the study was survival. Patients were initially randomized to docetaxel injection concentrate 100 mg/m^2 or best supportive care, but early toxic deaths at this dose led to a dose reduction to docetaxel injection concentrate 75 mg/m^2. A total of 104 patients were randomized in this amended study to either docetaxel injection concentrate 75 mg/m^2 or best supportive care.

In a second randomized trial (TAX320), 373 patients with locally advanced or metastatic non-small cell lung cancer, a history of prior platinum-based chemotherapy, and an ECOG performance status ≤2 were randomized to docetaxel injection concentrate 75 mg/m^2, docetaxel injection concentrate 100 mg/m^2 and a treatment in which the investigator chose either vinorelbine 30 mg/m^2 days 1, 8, and 15 repeated every 3 weeks or ifosfamide 2 g/m^2 days 1 to 3 repeated every 3 weeks. Forty percent of the patients in this study had a history of prior paclitaxel exposure. The primary endpoint was survival in both trials. The efficacy data for the docetaxel injection concentrate 75 mg/m^2 arm and the comparator arms are summarized in Table 15 and Figures 3 and 4 showing the survival curves for the two studies.

Reference ID: 3400944

Table 15 - Efficacy of Docetaxel Injection Concentrate in the Treatment of Non-Small Cell Lung Cancer Patients Previously Treated with a Platinum-Based Chemotherapy Regimen (Intent-to-Treat Analysis)

	TAX317		TAX320	
	Docetaxel 75 mg/m^2 n=55	**Best Supportive Care n=49**	**Docetaxel 75 mg/m^2 n=125**	**Control (V/I*) n=123**
Overall Survival Log-rank Test	p=0.01		p=0.13	
Risk Ratio[††], Mortality (Docetaxel: Control) 95% CI (Risk Ratio)	0.56 (0.35, 0.88)		0.82 (0.63, 1.06)	
Median Survival 95% CI	7.5 months** (5.5, 12.8)	4.6 months (3.7, 6.1)	5.7 months (5.1, 7.1)	5.6 months (4.4, 7.9)
% 1-year Survival 95% CI	37%**[†] (24, 50)	12% (2, 23)	30%**[†] (22, 39)	20% (13, 27)
Time to Progression 95% CI	12.3 weeks** (9.0, 18.3)	7.0 weeks (6.0, 9.3)	8.3 weeks (7.0, 11.7)	7.6 weeks (6.7, 10.1)
Response Rate 95% CI	5.5% (1.1, 15.1)	Not Applicable	5.7% (2.3, 11.3)	0.8% (0.0, 4.5)

* Vinorelbine/Ifosfamide
** $p \leq 0.05$; [†] uncorrected for multiple comparisons; [††] a value less than 1.00 favors docetaxel.

Only one of the two trials (TAX317) showed a clear effect on survival, the primary endpoint; that trial also showed an increased rate of survival to one year. In the second study (TAX320) the rate of survival at one year favored docetaxel injection concentrate 75 mg/m^2.

Figure 3 - TAX317 Survival K-M Curves - Docetaxel Injection Concentrate 75 mg/m^2 vs. Best Supportive Care

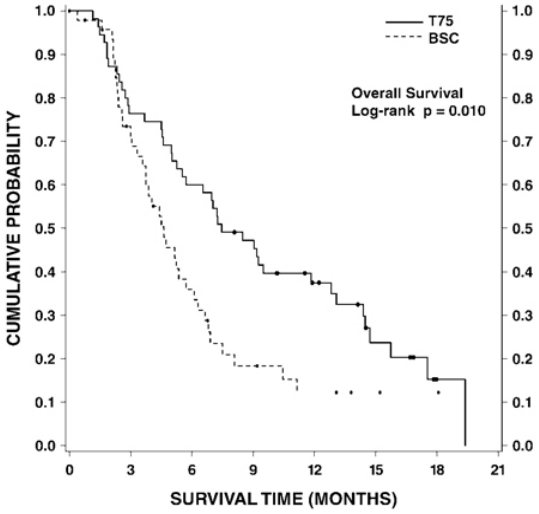

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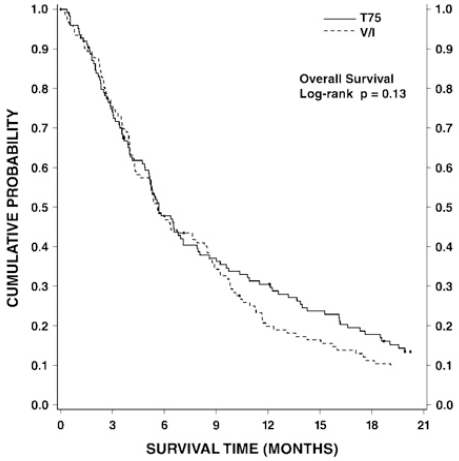
Figure 4 - TAX320 Survival K-M Curves - Docetaxel Injection Concentrate 75 mg/m^2 vs. Vinorelbine or Ifosfamide Control



Patients treated with docetaxel injection concentrate at a dose of 75 mg/m^2 experienced no deterioration in performance status and body weight relative to the comparator arms used in these trials.

Combination Therapy with Docetaxel Injection Concentrate for Chemotherapy-Naïve NSCLC

In a randomized controlled trial (TAX326), 1218 patients with unresectable stage IIIB or IV NSCLC and no prior chemotherapy were randomized to receive one of three treatments: Docetaxel injection concentrate 75 mg/m^2 as a 1 hour infusion immediately followed by cisplatin 75 mg/m^2 over 30 to 60 minutes every 3 weeks; vinorelbine 25 mg/m^2 administered over 6 to 10 minutes on days 1, 8, 15, 22 followed by cisplatin 100 mg/m^2 administered on day 1 of cycles repeated every 4 weeks; or a combination of docetaxel injection concentrate and carboplatin.

The primary efficacy endpoint was overall survival. Treatment with docetaxel injection concentrate+cisplatin did not result in a statistically significantly superior survival compared to vinorelbine+cisplatin (see table below). The 95% confidence interval of the hazard ratio (adjusted for interim analysis and multiple comparisons) shows that the addition of docetaxel injection concentrate to cisplatin results in an outcome ranging from a 6% inferior to a 26% superior survival compared to the addition of vinorelbine to cisplatin. The results of a further statistical analysis showed that at least (the lower bound of the 95% confidence interval) 62% of the known survival effect of vinorelbine when added to cisplatin (about a 2-month increase in median survival; Wozniak et al. JCO, 1998) was maintained. The efficacy data for the docetaxel injection concentrate+cisplatin arm and the comparator arm are summarized in Table 16.

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Table 16 - Survival Analysis of Docetaxel Injection Concentrate in Combination Therapy for Chemotherapy-Naïve NSCLC

Comparison	Docetaxel Injection Concentrate+Cisplatin n=408	Vinorelbine+Cisplatin n=405
Kaplan-Meier Estimate of Median Survival	10.9 months	10.0 months
p-value[a]	0.122	
Estimated Hazard Ratio[b]	0.88	
Adjusted 95% CI[c]	(0.74, 1.06)	

[a] From the superiority test (stratified log rank) comparing docetaxel injection concentrate+cisplatin to vinorelbine+cisplatin
[b]Hazard ratio of docetaxel injection concentrate+cisplatin vs. vinorelbine+cisplatin. A hazard ratio of less than 1 indicates that docetaxel injection concentrate+cisplatin is associated with a longer survival.
[c]Adjusted for interim analysis and multiple comparisons.

The second comparison in the same three-arm study, vinorelbine+cisplatin versus docetaxel injection concentrate+carboplatin, did not demonstrate superior survival associated with the docetaxel injection concentrate arm (Kaplan-Meier estimate of median survival was 9.1 months for docetaxel injection concentrate+carboplatin compared to 10.0 months on the vinorelbine+cisplatin arm) and the docetaxel injection concentrate+carboplatin arm did not demonstrate preservation of at least 50% of the survival effect of vinorelbine added to cisplatin. Secondary endpoints evaluated in the trial included objective response and time to progression. There was no statistically significant difference between docetaxel injection concentrate+cisplatin and vinorelbine+cisplatin with respect to objective response and time to progression (see Table 17).

Table 17 - Response and TTP Analysis of Docetaxel Injection Concentrate in Combination Therapy for Chemotherapy-Naïve NSCLC

Endpoint	Docetaxel Injection Concentrate+Cisplatin	Vinorelbine+Cisplatin	p-value
Objective Response Rate	31.6%	24.4%	Not Significant
(95% CI)[a]	(26.5%, 36.8%)	(19.8%, 29.2%)	
Median Time to Progression[b] (95% CI)[a]	21.4 weeks (19.3, 24.6)	22.1 weeks (18.1, 25.6)	Not Significant

[a]Adjusted for multiple comparisons.
[b]Kaplan-Meier estimates.

14.4 Hormone Refractory Prostate Cancer

The safety and efficacy of docetaxel injection concentrate in combination with prednisone in patients with androgen independent (hormone refractory) metastatic prostate cancer were evaluated in a randomized multicenter active control trial. A total of 1006 patients with Karnofsky Performance Status (KPS) ≥60 were randomized to the following treatment groups:

- Docetaxel injection concentrate 75 mg/m^2 every 3 weeks for 10 cycles.
- Docetaxel injection concentrate 30 mg/m^2 administered weekly for the first 5 weeks in a 6-week cycle for 5 cycles.
- Mitoxantrone 12 mg/m^2 every 3 weeks for 10 cycles.

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All 3 regimens were administered in combination with prednisone 5 mg twice daily, continuously.

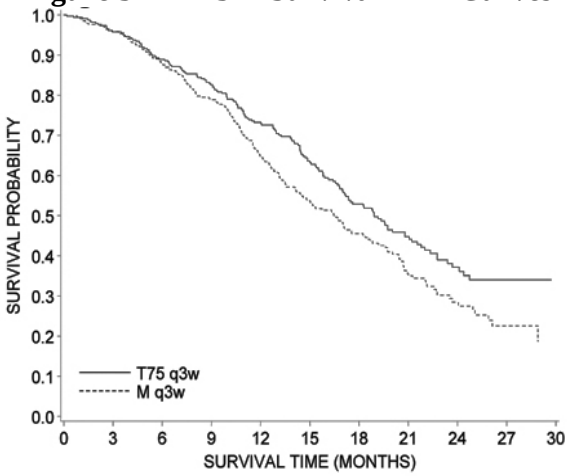
In the docetaxel injection concentrate every three week arm, a statistically significant overall survival advantage was demonstrated compared to mitoxantrone. In the docetaxel injection concentrate weekly arm, no overall survival advantage was demonstrated compared to the mitoxantrone control arm. Efficacy results for the docetaxel injection concentrate every 3 week arm versus the control arm are summarized in Table 18 and Figure 5.

Table 18 - Efficacy of Docetaxel Injection Concentrate in the Treatment of Patients with Androgen Independent (Hormone Refractory) Metastatic Prostate Cancer (Intent-to-Treat Analysis)

	Docetaxel Injection Concentrate+ Prednisone every 3 weeks	**Mitoxantrone+ Prednisone every 3 weeks**
Number of patients	335	337
Median survival (months)	18.9	16.5
95% CI	(17.0 to 21.2)	(14.4 to 18.6)
Hazard ratio	0.761	--
95% CI	(0.619 to 0.936)	--
p-value*	0.0094	--

*Stratified log rank test. Threshold for statistical significance = 0.0175 because of 3 arms.

Figure 5 -TAX327 Survival K-M Curves



14.5 Gastric Adenocarcinoma

A multicenter, open-label, randomized trial was conducted to evaluate the safety and efficacy of docetaxel injection concentrate for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for advanced disease. A total of 445 patients with KPS >70 were treated with either docetaxel injection concentrate (T) (75 mg/m^2 on day 1) in combination with cisplatin (C) (75 mg/m^2 on day 1) and fluorouracil (F) (750 mg/m^2 per day for 5 days) or cisplatin (100 mg/m^2 on day 1) and fluorouracil (1000 mg/m^2 per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The demographic characteristics were balanced between the two treatment arms. The median age was 55 years, 71% were male, 71% were Caucasian, 24% were 65 years of age or older,

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19% had a prior curative surgery and 12% had palliative surgery. The median number of cycles administered per patient was 6 (with a range of 1 to 16) for the TCF arm compared to 4 (with a range of 1 to 12) for the CF arm. Time to progression (TTP) was the primary endpoint and was defined as time from randomization to disease progression or death from any cause within 12 weeks of the last evaluable tumor assessment or within 12 weeks of the first infusion of study drugs for patients with no evaluable tumor assessment after randomization. The hazard ratio (HR) for TTP was 1.47 (CF/TCF, 95% CI: 1.19 to 1.83) with a significantly longer TTP (p=0.0004) in the TCF arm. Approximately 75% of patients had died at the time of this analysis. Overall survival was significantly longer (p=0.0201) in the TCF arm with a HR of 1.29 (95% CI: 1.04 to 1.61). Efficacy results are summarized in Table 19 and Figures 6 and 7.

Table 19 - Efficacy of Docetaxel Injection Concentrate in the treatment of patients with Gastric Adenocarcinoma

Endpoint	**TCF n=221**	**CF n=224**
Median TTP (months) (95%CI)	5.6 (4.86 to 5.91)	3.7 (3.45 to 4.47)
Hazard ratio† (95%CI) *p-value	0.68 (0.55 to 0.84) 0.0004	
Median survival (months) (95%CI)	9.2 (8.38 to 10.58)	8.6 (7.16 to 9.46)
Hazard ratio† (95%CI) *p-value	0.77 (0.62 to 0.96) 0.0201	
Overall Response Rate (CR+PR) (%)	36.7	25.4
p-value	0.0106	

*Unstratified log-rank test

†For the hazard ratio (TCF/CF), values less than 1.00 favor the docetaxel injection concentrate arm.

Subgroup analyses were consistent with the overall results across age, gender and race.

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Figure 6 -Gastric Cancer Study (TAX325) Time to Progression K-M Curve

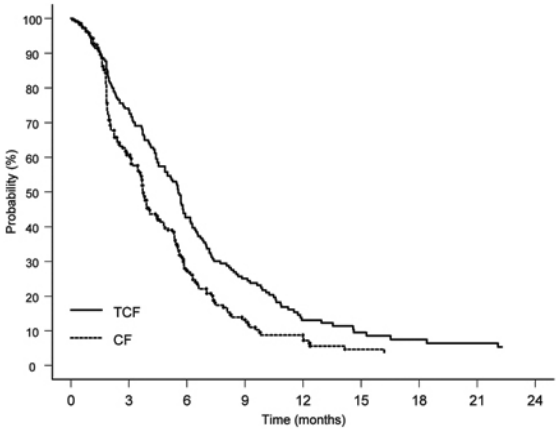
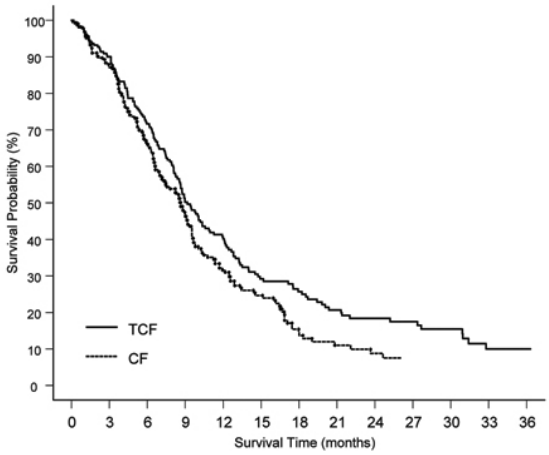


Figure 7 -Gastric Cancer Study (TAX325) Survival K-M Curve



14.6 Head and Neck Cancer

Induction chemotherapy followed by radiotherapy (TAX323)

The safety and efficacy of docetaxel injection concentrate in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a multicenter, open-label, randomized trial (TAX323). In this study, 358 patients with inoperable locally advanced SCCHN, and WHO performance status 0 or 1, were randomized to one of two treatment arms. Patients on the docetaxel injection concentrate arm received docetaxel injection concentrate (T) 75 mg/m^2 followed by cisplatin (P) 75 mg/m^2 on Day 1, followed by fluorouracil (F) 750 mg/m^2 per day as a continuous infusion on Days 1 to 5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines (TPF/RT). Patients on the comparator arm received cisplatin (P) 100 mg/m^2 on Day 1, followed by fluorouracil (F) 1000 mg/m^2/day as a continuous infusion on Days 1 to 5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received RT according to institutional guidelines (PF/RT). At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines. Locoregional therapy with radiation was delivered either with a conventional fraction regimen (1.8 Gy to 2.0 Gy once a day, 5 days per week for a total dose of 66 to 70 Gy) or with an accelerated/hyperfractionated regimen (twice a day, with a minimum interfraction interval of 6 hours, 5

days per week, for a total dose of 70 to 74 Gy, respectively). Surgical resection was allowed following chemotherapy, before or after radiotherapy.

The primary endpoint in this study, progression-free survival (PFS), was significantly longer in the TPF arm compared to the PF arm, p=0.0077 (median PFS: 11.4 vs. 8.3 months respectively) with an overall median follow up time of 33.7 months. Median overall survival with a median follow-up of 51.2 months was also significantly longer in favor of the TPF arm compared to the PF arm (median OS: 18.6 vs. 14.2 months respectively). Efficacy results are presented in Table 20 and Figures 8 and 9.

Table 20 - Efficacy of Docetaxel Injection Concentrate in the Induction Treatment of Patients with Inoperable Locally Advanced SCCHN (Intent-to-Treat Analysis)

Endpoint	**Docetaxel Injection Concentrate+ Cisplatin+ Fluorouracil n=177**	**Cisplatin+ Fluorouracil n=181**
Median progression free survival (months) (95%CI)	11.4 (10.1 to 14.0)	8.3 (7.4 to 9.1)
Adjusted Hazard ratio (95%CI) *p-value	0.71 (0.56 to 0.91) 0.0077	
Median survival (months) (95%CI)	18.6 (15.7 to 24.0)	14.2 (11.5 to 18.7)
Hazard ratio (95%CI) **p-value	0.71 (0.56 to 0.90) 0.0055	
Best overall response (CR + PR) to chemotherapy (%) (95%CI)	67.8 (60.4 to 74.6)	53.6 (46.0 to 61.0)
***p-value	0.006	
Best overall response (CR + PR) to study treatment [chemotherapy +/- radiotherapy] (%) (95%CI)	72.3 (65.1 to 78.8)	58.6 (51.0 to 65.8)
***p-value	0.006	

A Hazard ratio of less than 1 favors docetaxel injection concentrate+Cisplatin+Fluorouracil
* Stratified log-rank test based on primary tumor site
** Stratified log-rank test, not adjusted for multiple comparisons
*** Chi square test, not adjusted for multiple comparisons

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Figure 8 -TAX323 Progression-Free Survival K-M Curve

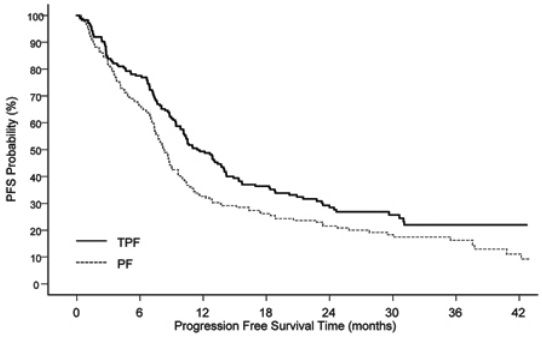
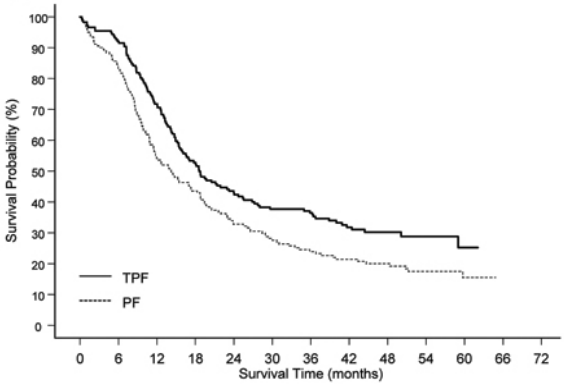


Figure 9 -TAX323 Overall Survival K-M Curve



Induction chemotherapy followed by chemoradiotherapy (TAX324)

The safety and efficacy of docetaxel injection concentrate in the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN was evaluated in a randomized, multicenter open-label trial (TAX324). In this study, 501 patients, with locally advanced SCCHN, and a WHO performance status of 0 or 1, were randomized to one of two treatment arms. Patients on the docetaxel injection concentrate arm received docetaxel injection concentrate (T) 75 mg/m² by intravenous infusion on day 1 followed by cisplatin (P) 100 mg/m² administered as a 30-minute to three-hour intravenous infusion, followed by the continuous intravenous infusion of fluorouracil (F) 1000 mg/m²/day from day 1 to day 4. The cycles were repeated every 3 weeks for 3 cycles. Patients on the comparator arm received cisplatin (P) 100 mg/m² as a 30-minute to three-hour intravenous infusion on day 1 followed by the continuous intravenous infusion of fluorouracil (F) 1000 mg/m²/day from day 1 to day 5. The cycles were repeated every 3 weeks for 3 cycles.

All patients in both treatment arms who did not have progressive disease were to receive 7 weeks of chemoradiotherapy (CRT) following induction chemotherapy 3 to 8 weeks after the start of the last cycle. During radiotherapy, carboplatin (AUC 1.5) was given weekly as a one-hour intravenous infusion for a maximum of 7 doses. Radiation was delivered with megavoltage equipment using once daily fractionation (2 Gy per day, 5 days per week for 7 weeks for a total dose of 70 to 72 Gy). Surgery on the primary site of disease and/or neck could be considered at anytime following completion of CRT.

The primary efficacy endpoint, overall survival (OS), was significantly longer (log-rank test, p=0.0058) with the docetaxel injection concentrate-containing regimen compared to PF [median OS: 70.6 versus

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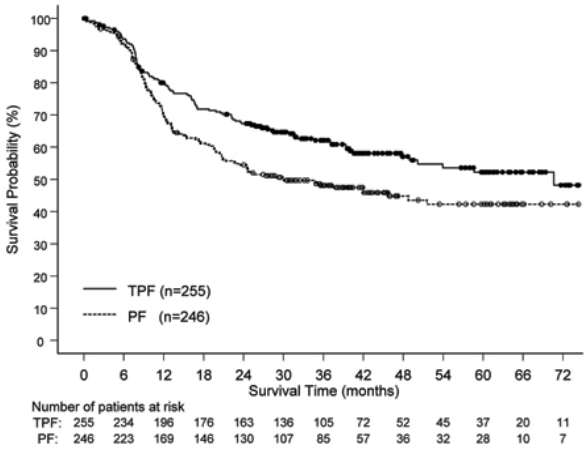
30.1 months respectively, hazard ratio (HR)=0.70, 95% confidence interval (CI)= 0.54 – 0.90]. Overall survival results are presented in Table 21 and Figure 10.

Table 21 - Efficacy of Docetaxel Injection Concentrate in the Induction Treatment of Patients with Locally Advanced SCCHN (Intent-to-Treat Analysis)

Endpoint	Docetaxel Injection Concentrate+ Cisplatin+Fluorouracil n=255	Cisplatin+ Fluorouracil n=246
Median overall survival (months) (95% CI)	70.6 (49.0 to NE)	30.1 (20.9 to 51.5)
Hazard ratio: (95% CI) *p-value	0.70 (0.54 to 0.90) 0.0058	

A Hazard ratio of less than 1 favors docetaxel injection concentrate+cisplatin+fluorouracil
* un-adjusted log-rank test
NE - not estimable

Figure 10 - TAX324 Overall Survival K-M Curve



15. REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

3. American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling Hazardous Drugs. Am J Health-Syst Pharm. 2006;63:1172-1193

4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

One-vial Docetaxel Injection Concentrate

Docetaxel injection concentrate is supplied as a sterile, pyrogen-free, non-aqueous solution in single-use, flip-top glass vials, as a clear, viscous, colorless to pale yellow solution, without macroscopic particles in solution at 20 mg/mL concentration in the following package strengths:

Docetaxel injection concentrate 20 mg/mL	NDC 45963-734-54
Docetaxel injection concentrate 80 mg/4 mL (20 mg/mL)	NDC 45963-734-52
Docetaxel injection concentrate 140 mg/7 mL (20 mg/mL)	NDC 45963-734-74

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Retain in the original package to protect from light.

16.3 Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published *[see References (15)]*.

17. PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information)

- Docetaxel injection concentrate may cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug. Women of childbearing potential should use effective contraceptives if receiving docetaxel injection concentrate [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)]*.
- Obtain detailed allergy and concomitant drug information from the patient prior to docetaxel injection concentrate administration.
- Explain the significance of oral corticosteroids such as dexamethasone administration to the patient to help facilitate compliance. Instruct patients to report if they were not compliant with oral corticosteroid regimen.
- Instruct patients to immediately report signs of a hypersensitivity reaction.
- Tell patients to watch for signs of fluid retention such as peripheral edema in the lower extremities, weight gain and dyspnea.
- Explain the significance of routine blood cell counts. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever.
- Instruct patients to report myalgia, cutaneous, or neurologic reactions.
- Explain to patients that side effects such as nausea, vomiting, diarrhea, constipation, fatigue, excessive tearing, infusion site reactions, and hair loss are associated with docetaxel administration.

Sterile, Nonpyrogenic, Preservative-free.
The container closure is not made with natural rubber latex.

Rx Only

Reference ID: 3400944

Manufactured by:
Sindan Pharma SRL
11 Ion Mihalache Blvd
Bucharest 1, Romania 011171

Distributed by:
Actavis Inc.
60 Columbia Rd., Bldg B.
Morristown, NJ 07960 USA

Revised – November 2013

Reference ID: 3400944